

Remarks

After entry of the amendment, Claims 35-50 are pending.

Claims 35, 41, 45, and 48 have been amended and remain supported by the specification.

Claims 51-53 have been canceled without prejudice.

Applicants respectfully request entry of this amendment because it places the application in better form for appeal or places the application in condition for allowance.

No issues of new matter should arise and entry of the amendment is respectfully requested.

Rejections under 35 USC § First Paragraph

Claims 45-53 are rejected under 35 USC § 112, first paragraph, as lacking an adequate written description and as lacking enablement.

Applicants respectfully traverse the rejection.

I. Claims 45-50

Applicants have provided an adequate written description of the claimed invention and a skilled artisan could practice the claimed invention without undue experimentation as discussed below.

Claims 45-47 recite that the peptide has at least 95% sequence identity to a GLP-1 peptide comprising the amino acid sequence of SEQ ID NO. 3. GLP-1 has 30 amino acids, such that 95% sequence identity means that the claimed peptide differs by one amino acid (e.g., by addition, deletion, or substitution).

Claims 48-50 recite that the peptide has at least 90% sequence identity to a GLP-1 peptide comprising the amino acid sequence of SEQ ID NO. 3. The GLP-1 peptide of SEQ ID NO. 3 comprises 30 amino acids, such that 90% sequence identity means that the claimed peptide differs by one, two, or three amino acids (e.g., by addition(s), deletion(s), substitution(s), or combinations thereof).

The disclosure of SEQ ID NO. 3 combined with the knowledge in the art regarding the genetic code and its redundancies would have put one in possession of the claimed peptides. With the aid of a computer, the skilled artisan could identify every peptide with at least 90% or

95% sequence identity to SEQ ID NO. 3. Thus, Applicant was in possession of the claimed invention at the time the application was filed.

At page 6 in the Office Action, the PTO asserts that the specification does not describe where changes can be made in the amino acid sequence of SEQ ID NO:3 without changing the function of the peptide. The PTO's position is contrary to the explicit teachings in the specification, as discussed below.

At Paragraph Nos. 98-109, the specification provides numerous examples of peptides having at least 90% or at least 95% sequence identity to a GLP-1 peptide comprising the amino acid sequence of SEQ ID NO. 3. The specification provides detailed teachings and guidance as to particular substitutions, deletions, insertions and combinations thereof that could be made to a GLP-1 peptide comprising the amino acid sequence of SEQ ID NO. 3. to produce peptides having at least 90% or at least 95% sequence identity to the GLP-1 peptide and that have GLP-1 activity. For example, Paragraph No. 105 in the specification teaches:

The analogs of the invention which show enhanced insulin stimulating properties have the foregoing sequence, or the C-terminal amide thereof, with at least one modification of SEQ ID NO:75 [*which includes GLP-1 of SEQ ID NO:3*], selected from the group consisting of:
(a) substitution of a neutral amino acid, arginine, or a D form of lysine for lysine at position 26 and/or 34 and/or a neutral amino acid, lysine, or a D form of arginine for arginine at position 36;

(b) substitution of an oxidation-resistant amino acid for tryptophan at position 31;

(c) substitution according to at least one of:

Y for V at position 16;

K for S at position 18;

D for E at position 21;

S for G at position 22;

R for Q at position 23;

R for A at position 24; and

Q for K at position 26;

(d) a substitution comprising at least one of:

an alternative small neutral amino acid for A at position 8;

an alternative acidic amino acid or neutral amino acid for E at position 9;

an alternative neutral amino acid for G at position 10; and

an alternative acidic amino acid for D at position 15; and

(e) substitution of an alternative neutral amino acid or the D or N-acylated or alkylated form of histidine for histidine at position 7.

As another example, Paragraph No. 107 in the specification teaches:

In another aspect, the invention is directed to peptides which show enhanced degradation resistance in plasma as compared to GLP-1 (7-37) wherein this enhanced resistance to degradation is defined as set forth below. In these analogs, any of the above-mentioned truncated forms of GLP-1 (7-34) to GLP-1 (7-37) or their C-terminal amidated forms [*which includes GLP-1 of SEQ ID NO:3*] is modified by

- (a) substitution of a D-neutral or D-acidic amino acid for H at position 7, or
- (b) substitution of a D-amino acid for A at position 8, or
- (c) both, or
- (d) substitution of an N-acylated or N-alkylated form of any naturally occurring amino acid for H at position 7.

At Examples 1-3, the specification provides experiments that can be performed to determine if any particular peptide functions like GLP-1, such that the skilled artisan could easily determine without undue experimentation if a peptide having at least 90% or at least 95% sequence identity to the GLP-1 peptide functions in a manner similar to GLP-1.

Based on the numerous examples of peptides having at least 90% and at least 95% sequence identity to a GLP-1 peptide comprising the amino acid sequence of SEQ ID NO. 3; the guidance and teachings provided in the specification as to modifications that can be made to GLP-1; and the experiments that can be used to determine the activity of GLP-1, Applicants respectfully submit that Claims 45-50 satisfy the written description requirement and the enablement requirement under 35 USC § 112, first paragraph.

In view thereof, Applicants respectfully request that the rejection be withdrawn.

II. Claims 51-53

Claim 51-53 have been canceled without prejudice, rendering the rejection of these claims moot.

III. The Office Action: Written Description

At page 4 in the Office Action, the PTO states:

...The claims are drawn to method of alleviating a condition or disorder associated with toxic hypervolemia in an individual, comprising administering to said individual a therapeutically effective amount of a GLP-1 or GLP-1 agonist analog or derivative.

This statement is wrong. First, the pending claims are NOT directed to a “method of alleviating a condition or disorder associated with toxic hypervolemia.” Second, the pending claims are NOT directed to administering “a GLP-1 or GLP-1 agonist analog or derivative.” It is impossible for prosecution of this application to proceed in a fair and efficient manner if the PTO is not examining the pending claims.

At Page 5 in the Office Action, the PTO states:

...unquestionable that claim 5 are a broad generic, with respect to all possible compounds encompassed by the claims and possible conditions and disorders. The possible structural variations are limitless to any class of analog or derivative. Further, the conditions associated with toxic hypervolemia are also limitless as it needs not be caused by toxic hypervolemia but nearly associated.

This statement is wholly unrelated to the pending claims. First, Claim 5 is NOT pending in the application. Second, the possible number of compounds encompassed by a peptide having at least 90% or 95% sequence identity to the GLP-1 peptide comprising the amino acid sequence of SEQ ID NO:3 is NOT limitless. The claims encompass peptides that differ from the amino acid sequence of SEQ ID NO:3 by only one, two, or three amino acids. Finally, the claims are NOT directed to conditions associated with toxic hypervolemia. The Claims recite methods of treating hypertension. It is impossible for prosecution of this application to proceed in a fair and efficient manner if the PTO is not examining the pending claims.

At Page 4, Part (2), in the Office Action, the PTO provides a discussion of proglucagon (PG) which is unrelated to the pending claims. The pending claims are directed to GLP-1 peptides comprising the amino acid sequence of SEQ ID NO:3 and to peptides having at least 90% or at least 95% sequence identity thereto. Proglucagon (PG) is not relevant to the pending claims and it is impossible to understand how this discussion in the Office Action has any relevance to the rejection of the claims under the written description requirement.

It is incumbent on the PTO to analyze the pending claims. Applicants cannot respond to a rejection that is not based on the claims pending in the application. The PTO has not established a *prima facie* rejection for lack of written description under § 112, first paragraph, because the PTO is not even reviewing the pending claims.

IV. The Office Action: Enablement

At pages 11-12 in the Office Action, the PTO refers to Schinzel et al, *FEBS*, 286:125-128 (1991) as the state of the art. Schinzel is a paper that is directed to a study of two amino acid substitutions in the phosphate recognition site of *Escherichia coli* maltodextrin phosphorylase. The PTO has not provided any explanation as to how the *Escherichia coli* maltodextrin phosphorylase active site is representative of the entire art of peptide/protein chemistry and has not provided any reason why or how the skilled artisan would expect a paper describing two amino acid substitutions in the *Escherichia coli* maltodextrin phosphorylase active site to be related to GLP-1. There is no evidence of any relationship between the *Escherichia coli* active site in Schinzel and the GLP-1 peptides in the claimed invention that would establish Schinzel as representative of the state of the entire art.

Assuming, *arguendo*, that Schinzel is representative of the art, Schinzel provides evidence that it would not require undue experimentation to determine how or whether a change in a single amino acid would impact the function of the protein/peptide. Schinzel provides evidence that simple experimental process that are well known in the art can be used to determine how amino acid substitutions would affect the *Escherichia coli* maltodextrin phosphorylase active site. Schinzel did nothing more than (1) change an amino acid in the *Escherichia coli* maltodextrin phosphorylase active site and (2) test the resulting protein in an enzyme activity assay. This is routine experimentation, and demonstrates that if Schinzel is representative of the art, the skilled artisan could practice the presently claimed invention without undue experimentation.

Other scientific papers, that show the state of the art, teach that amino acid substitutions do not change the activity of the peptide, such as Strom et al, *The Journal of Biological Chemistry*, 266(3):1656-1664 (1991) (attached as Exhibit A); and Tugyi et al, "Partial D-amino acid substitution: Improved enzymatic stability and preserved Ab recognition of a MUC2 epitope peptide," *PNAS*, 102(2):413-418 (2005) (attached as Exhibit B).

In the Abstract, Strom teaches:

A total of 37 separate mutants containing single and multiple amino acid substitutions in the leader and amino-terminal conserved region of the Type IV pillin from *Pseudomonas aeruginosa* were

generated by oligonucleotide-directed mutagenesis. The effect of these substitutions on the secretion, processing, and assembly of the pilin monomers into mature pili was examined. The majority of substitutions in the highly conserved amino-terminal region of the pilin monomer had no effect on pilation. Likewise, substitution of several of the residues within the six amino acid leader sequence did not affect secretion and leader cleavage (processing), including replacement of one or both of the positively charged lysine residues with uncharged or negatively charged amino acids.

In the second paragraph on page 1662, Strom states:

A striking feature of the study presented here is the extent of amino acid substitutions of the pilin polypeptide that have little or no effect on pilus biogenesis.

Like Schinzel, Strom did nothing more than (1) change amino acids in the amino-terminal conserved region of the Type IV pillin from *Pseudomonas aeruginosa* and (2) test the resulting protein in an assay. Based on the PTO's enablement analysis in the Office Action, Strom provides evidence that the presently claimed invention is enabled.

Tugyi teaches that amino acid substitutions in the MUC2 peptide improved the enzymatic stability of the peptide. At page 418, right column, Tugyi teaches:

Together, our results indicate that the epitope function ... of peptide ¹⁵TPPTGTQTPT²⁵ is retained even in the presence of two D-amino acid residues at its N-terminal flanking region, and up to three at its C-terminal flanking region (tpTPTGTQtp). This substituted peptide also shows high resistance against proteolytic degradation in diluted human serum and in lysosomal preparation.

Like Schinzel, Tugyi did nothing more than (1) change amino acids in the MUC2 peptide and (2) test the resulting peptide in an assay. Tugyi provides evidence that the presently claimed invention is enabled.

Obviousness-Type Double Patenting Rejection

Claims 35-53 are rejected on the ground of nonstatutory obviousness-type double patenting over Claims 5 and 7 of US Patent No. 6,703,359 (the '359 patent).

Applicants respectfully traverse the rejection to the extent the obviousness-type double patenting rejection is based on Claims 5 and 7 in the '359 patent. Exendin is NOT a derivative

or analog of GLP for the reasons set forth in the Response filed March 7, 2008, which is incorporated by reference herein in its entirety.

In view of Claim 40 in the '359 patent (and optionally further in view of Claim 7 to the extent that Claim 7 recites that hypertension is a condition or disorder associated with toxic hypervolemia), Applicants are submitting a Terminal Disclaimer.

In view thereof, Applicants respectfully request that the obviousness-type double patenting rejection be withdrawn.

Conclusion

Applicants respectfully request an early and favorable reconsideration and allowance of Claims 35-50.

Respectfully submitted,

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